Transfusion Medicine Reviews

# The difference in potential harms between whole blood and component blood transfusion in major bleeding: a rapid systematic review and meta-analysis of RCTs

## HIGHLIGHTS

- Only very-low quality evidence is available for benefit and harms of WB vs BC
- No differences between WB and blood components for mortality (very low certainty)
- WB may reduce length of hospitalisation (non-trauma subgroup) (very low certainty)
- WB may reduce length of oxygen therapy (non-trauma subgroup) (very low certainty)

# The difference in potential harms between whole blood and component blood transfusion in major bleeding: a rapid systematic review and metaanalysis of RCTs

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## ABSTRACT

Our aim was to assess whether there is a difference in outcomes of potential “all-cause” harm in the transfusion of whole blood (WB) compared to blood components (BC) for any bleeding patient regardless of age or clinical condition.

We searched multiple electronic databases using a pre-defined search strategy from inception to 2nd March 2021. One reviewer screened, extracted, and analysed data, with verification by a second reviewer of all decisions. We used Cochrane ROB1 and GRADE to assess the quality of the evidence.
We used predefined subgroups of trauma and non-trauma studies in the analysis.

We included six RCTs (618 participants) which compared WB and BC transfusion therapy in major bleeding, one trauma trial (n=107), and five surgical trials (non-trauma) (n=511).

We GRADED evidence as very-low for all outcomes (downgraded for high and unclear risk of bias, small sample size, and wide confidence intervals around the estimate).

Our primary outcome (all-cause mortality at 24-hours and 30-days) was reported in 3 out of 6 included trials. There was no evidence of a difference in mortality of WB compared to BC therapy (very-low certainty evidence).

There may be a benefit of WB therapy compared to BC therapy in the non-trauma subgroup, with a reduction in the duration of oxygen dependence (1 study; n=60; mean difference 5.9 fewer hours [95% Confidence Interval [CI] -10.83, -0.99] in WB group), and a reduction in hospital stay (1 study, n=64, median difference 6 fewer days in WB group) (very-low certainty evidence).

For the remaining outcomes (organ injury, mechanical ventilation and intensive care unit requirement, infection, arterial/venous thrombotic events, and haemolytic transfusion reaction) there was no difference between WB and BC therapy (wide CI, crossing line of no effect), though many of these outcomes were based on small single studies (very-low certainty evidence).

In conclusion, there appears to be little to no difference in harms between WB and BC therapy, based on small studies with very low certainty of the evidence. Further large trials are required to establish the overall safety of WB compared to BC, and to assess differences between trauma and non-trauma patients.

## INTRODUCTION

### Description of the condition

Management of bleeding that requires blood transfusion can occur in any clinical setting. Treatment with a blood transfusion is a lifesaving intervention and can be delivered as a Whole Blood (WB) component or as different blood components that are derived from WB or apheresis: these include red blood cells (RBC), platelets or plasma, however all these components are stored at different temperatures. The RBC are stored at 4°C, platelets are stored at room temperatures under constant agitation, while plasma is

rapidly frozen to ≤25°C to produce fresh frozen plasma (FFP). Another blood component that is derived from FFP following slow thawing is cryoprecipitate (rich in FVIII, von Willebrand factor, FXIII, fibronectin and fibrinogen) that is also stored at ≤25°C [1].

The fresh WB component (fresh WB) is transfused to patients within 24 hours of it being donated. It was used routinely by the military to provide haemostatic resuscitation for bleeding soldiers during World War I and II and Korean and Vietnam Wars, and this component continues to be used in recent conflicts. One recent systematic review identified 27 studies between 2006 and 2020 that had reported on >10,000 transfusions of fresh WB units in different countries, showing equivalent survival for fresh WB resuscitation compared with component therapy [2].

By 1965 the use of fresh WB reduced significantly, due to the introduction of blood components (i.e., RBC, FFP, Platelet), which made the logistics of supply and demand more manageable for the blood manufacturing units, as blood components had longer shelf-lives compared with fresh WB. Furthermore, availability of blood components allowed for targeted replacement therapy of missing clotting factors, particularly in haemophilia patients, and in so doing it minimised the potential risks and side effects of receiving unneeded blood components.

In recent years, there has been an increased interest in the use of WB transfusion to resuscitate bleeding patients associated with trauma, with studies now demonstrating that early and continuous support with RBC, plasma and platelet transfusions (mimicking WB) in a 1-1-1 ratio could improve survival [3–5]. This has resulted in some blood services introducing a WB component that is stored at 4°C for a longer period (or stored WB) than fresh WB to treat bleeding patients associated with trauma, particularly outside the hospital environment [6–8]. A recent systematic review (SR) [9] that compared the impact of WB transfusion versus blood component therapy on 30-day mortality for adult trauma patients with acute major haemorrhage, identified six studies involving a total of 3,255 patients, of which only one small study was a randomised control trial (RCT) (n=107 patients): the SR found no evidence of benefits or harm with the use of WB transfusion.

If the results of the above clinical studies show that stored WB is superior to components therapy, then the issue of whether stored WB can be used for other clinical settings becomes very important. This is because if stored WB is used only for a small sub-group of patients with bleeding, trauma patients, it would undoubtedly result in significantly increased blood wastage [10], unless stored WB is re-manufactured back to RBC later in its shelf-life [8], or it is transfused to other patients with bleeding.

**Why it is important to do this review**

There have been a few systematic reviews in the use of WB in trauma setting [2,9], but none in other settings. If WB component therapy is to be introduced into routine care, it will not be sustainable for any blood service to utilise this component for one patient group (trauma patients), and its use in other settings for management of major bleeding would reduce blood wastage (as seen with component therapy experiences), without incurring significant costs.

**Objective**

Prior to the widespread use of WB transfusion into routine care, we would want to establish the evidence on its overall safety (including blood safety outcomes) versus components therapy in all major bleeding settings. Therefore, the objective of this rapid systematic review (RSR) is to assess whether there is a difference in potential "all-cause" harms (including transfusion-related complications as well as other harms that may not usually be attributed to the transfusion) when giving WB compared to BC to any bleeding patient regardless of age or clinical condition.

## METHODS

The protocol for this review was prospectively registered on PROSPERO [PROSPERO 2021 CRD42021242255], and the review was carried out in accordance with the Cochrane guidelines for Rapid Reviews [11] and PRISMA [12].

### Study Selection

We included randomised controlled trials (RCTs), including cluster RCTs and quasi RCTs, and Systematic Reviews (SRs) of RCTs that assessed all patients (adults and children) presenting with any type of major bleeding (as defined in the study). We included trials that compared *fresh or stored Whole Blood* (WB) (containing RBC, plasma, and platelets) from allogeneic donors with blood component therapy (red blood cells (RBC), and/or any forms of plasma (like thawed frozen plasma, lyophilised plasma or pathogen-inactivated plasma), and/or platelets (pathogen or non-pathogen inactivated) and/or cryoprecipitate (pathogen or non-pathogen inactivated), or standard care (as defined by the hospital/study). We excluded trials of autologous WB transfusion, as this is donated back to the donor and thus is unlikely to lead complications.

We excluded studies that did not report any of the pre-specified review outcomes. However, we tabulated these studies and documented whether they had reported any of the following outcomes: blood loss; bleeding time; additional blood/blood product requirement; re-operation required.

### Outcomes

Due to the severe trauma/surgical complexities experienced by the patients of interest in this review, we realised that assessing transfusion-related safety outcomes alone would not give the complete picture of safety data when comparing WB and BC transfusion. For this reason, we included a broader definition of safety, beyond those outcomes that can be diagnosed as transfusion-related (e.g. TRALI, TAD, TACO, anaphylaxis): thus, we also assessed mortality and organ injury, that may not otherwise be attributed to the transfusion itself.

Therefore, our primary outcome was all-cause mortality (24 hours and 30 days). Secondary outcomes included: organ injury (acute kidney failure: acute renal injury, dialysis, or kidney failure; heart failure or transfusion-related circulatory overload (TACO); lung injury: transfusion related acute lung injury (TRALI), transfusion associated dyspnoea (TAD), acute respiratory distress syndrome (ARDS); liver failure); anaphylaxis or severe allergic reaction (leading to increased respiration or Epi-Pen requirement); length of hospitalisation; requirement for mechanical ventilation and intensive care (ICU) (including critical care units); infection requiring treatment (e.g. antibiotics, antifungals); any arterial

or venous thrombotic event (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism); and haemolytic transfusion reactions (this was included after registration on PROSPERO).

**Searches**

A single author (CD) searched electronic databases (CENTRAL, Embase, MEDLINE, Transfusion
Evidence Library, and PubMed) for RCTs and systematic reviews of RCTs from database inception to 2nd March 2021, using a pre-defined search strategy (see Supplementary Information for search strategy).

No restrictions were imposed on language or publication date. We did not search for ongoing trials, trial protocols, SR protocols, or other grey literature.

We hand-searched the reference lists of included studies and relevant SRs to identify further relevant studies.

**Data collection and analysis**

We used Endnote software for initial screening (title and abstract), and full text assessment. Two reviewers (LJG, SJB) performed dual screening, with conflict resolution through discussion, or arbitration with another author (LJE/LGr) where necessary. One reviewer (LJG) screened all included full-text publications, and a second reviewer (SJB) verified the reason for exclusion for all studies.

***Data extraction and management***

Data extraction was performed by a single author (LJG) with verification by a second author (SJB), arbitration by a third author was not necessary. Information was collected from the studies selected for inclusion using a standardised data collection form (in Excel), with the principal outcomes of mortality and harms (organ injury). We also double-checked our ROB assessment and extracted data against other published SRs from our search that had examined the same RCTs.

***Dealing with missing data***

We did not actively seek missing data from trial authors as this is a rapid review. Where possible, we analysed data on an intention-to-treat basis, though it was only assumed to be ITT for some studies due to unclear reporting.

***Assessment of ROB in included studies***

A single author (LJG) (with verification by second author (SJB)) used a Cochrane risk of bias assessment tool (ROB1) according to Higgins [13]. We have presented a Risk of bias graph and a Risk of bias summary figure (see Supplementary Tables s1 and s2).

***Data synthesis***

We were able to combine studies into a single comparison of WB versus BC therapy. We used RevMan to calculate odds ratios (OR) and 95% confidence interval (CI) for dichotomous outcomes, and mean difference and 95% CI for continuous outcomes. Only length of hospitalisation, mechanical ventilation, and intensive care unit (ICU) stay were continuous and are reported as mean (standard deviation [SD]) and median (interquartile range [IQR]) or median [range]). We did not convert medians into another form and have presented data as reported by the studies.

We used the $I^2$ statistic to quantify the possible degree of heterogeneity of treatment effects between trials. We used a random-effects model due to the nature of the studies (except where we have used Peto OR for low event rates). We grouped studies by trauma/non-trauma where this was possible.

A single reviewer (LJG) assessed the certainty of the evidence using GRADE with verification of all judgements (and footnoted rationale) by second reviewer (SJB). Outcomes reported as median and IQR/range were assessed using GRADE as single studies to also assess the quality and certainty of the evidence. Arbitration by a third author was unnecessary.

Where meta-analysis was not possible (data reported as median and IQR/range), we have presented results in descriptive tables by condition and intervention type, and the main findings.

***Assessment of reporting bias***

It was not possible to assess publication bias due to the small number of trials included (less than 10).

***Subgroup and sensitivity analyses***

We subgrouped data by trauma and non-trauma (surgery) only. Sensitivity analyses were not performed due to the small number of trials.

# RESULTS

## Study selection

After removal of duplicates, we screened 1821 references based on the title and abstract, and excluded 1770 references (Figure 1). We screened 51 full text articles and excluded 43 (Table s1): 20 were systematic or narrative reviews; five did not report review outcomes (Table s2); two are ongoing trials, T-STORHM and PPOWER (Table s3); and one study did not compare WB to blood components (Jensen 1992 [21]; 4 publications), instead it compared unfiltered WB to filtered (leucocyte reduced) WB.

We included six studies from eight publications in the narrative synthesis and meta-analyses (Figure
1).

## Study Characteristics

Six RCTs totalling 618 participants fulfilled our predefined criteria [14–19]. Five trials were RCTs and one trial was a quasi-RCT [17].

Trials were published between 1975 and 2021. Three trials were from the USA [14,17,18], one from Canada [15], one from India [19], and one from Germany [16]. All were single-centre trials, when reported. Funding was reported by five trials [14,15,17–19]. Two were funded through USA military grants [14,18], and three were funded through hospital research funds [15,17,19]. One trial did not report funding [16]. There were no obvious conflicts of interest.

Trials varied in size from 28 [18] to 294 participants [17]. Most trials randomised approximately 60 participants. Only one study reported that they had reached the sample size necessary to sufficiently power their primary outcome (chest tube volume loss [15]). One study did not meet their calculated requirement (n=66 per group required, [14]), and four studies [16–19] did not report a power calculation or minimum sample size required.

One trial examined major bleeding due to trauma [14]. The remaining five trials assessed patients undergoing non-trauma surgery: cardiac surgery with cardiopulmonary bypass (CPB) [15][16]; aortic reconstruction [18]); elective spinal deformity surgery [19]; and any elective surgery without CPB [17]. Participant age varied between trials. The youngest participants were less than one month of age [15] and the oldest participants averaged 58 to 60 years of age [18].

## Comparison (whole blood versus blood component)

All six trials could be combined into a single comparison that examined WB compared to BC therapy, which we sub-grouped by traumatic or non-traumatic bleeding. The

intervention and comparator groups are described briefly below and in Table 1 (study characteristics), with further detail in the Supplementary Information (Table s4).

The type of WB used in the two oldest trials was not reported, but we have assumed that it was not leucocyte depleted, as this was not a common practise at this time [17,18]. The three most recent trials stated that the WB was "filtered" or leucocyte-reduced WB [14,15,19]. Due to insufficient information within the publication, it was not possible to identify whether Moritz 2000 [16] filtered the WB, referring to it as "fresh whole blood". See Supplementary Table s4 for further detail.

Blood component therapy differed significantly between studies and is described briefly in Table 1, with further detail in Supplementary Table s4.

## Outcomes

Our primary outcome of mortality was reported in 3 of 6 studies (24-hour mortality [14,15]; 30-day mortality [14,15,17]).

The most reported outcome of interest for this review was ICU/high dependency unit (HDU) length of stay [14–16,19], however this was largely reported as median and IQR or range, and so could not be meta-analysed. No study reported anaphylaxis or allergy.

Length of stay (LOS) outcomes (hospitalisation, mechanical ventilation, ICU/HDU stay) were reported by one study [14] as hospital-free days, ventilator-free days, ICU-free days. However, due to the follow up study period being limited to 30 days (not explicitly stated, but all upper ranges did not go beyond 30 days, and other reviews that extracted data from this paper have stated the follow up period was only 30 days [20]), we were able to take the reverse of these data, and have reported them as required for our analyses.

## Risk of bias in included studies

An overview of risk of bias by study and by risk of bias domain can be seen in Supplementary information (Figures s1 and s2).

### *Selection bias (random sequence generation and allocation concealment)*

One study [17] was at high risk of bias, as they used the final digit (odd/even) of the patient identification number to assign treatment groups (quasi-RCT). We classified the remaining studies at unclear risk of bias due to a lack of clear descriptions of random sequence generation or allocation concealment, or both.

### *Performance bias and detection bias (blinding of patients and personnel)*

Blinding was largely not reported in included studies. Only one study [15] reported that surgeons were blinded to allocation, but post-operative care staff were unblinded, which could have impacted on some outcome measures; this is unlikely due to the nature of the

objective outcomes we are assessing. Cotton 2013[14] also reported on blinding, stating that blinding was broken once the blood cooler seal was broken, strongly suggesting that the participating surgeons and clinicians were aware of allocation both during and after any treatment.

***Attrition bias (incomplete outcome data)***

Only two studies [14,17] stated the data presented were intention-to-treat (ITT), and provided information on participant flow, including information on drop-out and loss to follow up, and were assessed as low ROB. Cotton 2013 [14] also provided per-protocol (PP) data in a secondary publication [21]. The remaining four trials did not report participant flow, and ITT was assumed for purposes of analysis, and were assessed as unclear ROB.

***Reporting bias (selective reporting)***

Only one of the six included studies [14] could be checked for reporting bias through the trial registration, and was assessed as low ROB. The remaining five studies were assessed as unclear.

***Other bias (funding and baseline imbalances)***

One study had high risk of bias due to severe baseline imbalance [14] with significantly greater number of patients in the WB group with nonsurvivable traumatic brain injury (TBI) despite randomisation and blinded group assignment. Two studies [16,17] did not report on funding or baseline imbalances, and so ROB was deemed unclear. The remaining studies had low risk of bias.

## Effects of intervention: Whole blood (WB) versus blood component (BC) therapy

Certainty of the evidence for all outcomes was assessed as very-low using GRADE for randomised studies. See Table 2 (overview of results) and supplementary Figure s3 (forest plots), Table s5 (overview of results, in colour), and Table s6 (GRADE table) for further detail.

***Primary outcome: All-cause mortality (Figure 2)***

There was no evidence of effect (95% CI crossed the line of no effect representing both benefit and harm as a result of the intervention) in trauma and non-trauma (surgery) patients for 24-hour (2 studies, n=171) and 30-day mortality (3 studies, n=465). Data for 30-day mortality showed a small difference in direction of effect by subgroup (trauma compared to non-trauma (Figure 2), but this did not reach significance. This difference may be due to known baseline imbalances in the single trauma study (nonsurvivable TBI higher in WB group accounting for 60% of WB vs 33% of BC patients (P = 0.29) [14]).

***Secondary outcome: Harms (adverse events)***

No data were available for the incidence of patients experiencing anaphylaxis or allergy.

**Organ injury (Figure 3):** There was no evidence of a difference in organ injury reported in trauma patients (1 study, n=107) including: kidney injury (acute kidney injury/acute renal failure); heart injury (congestive heart failure, arrhythmia); and lung injury (TRALI, ARDS). A single study of nontrauma patients reported zero cases of pulmonary oedema (lung injury) in both WB and BC groups (1 study, n=28), no other organ injury outcomes were reported. (Figure 3 and supplementary figure s3.b).

**Hospitalisation (length of stay):** Two trials (n=171), one trauma (n=107) and one non-trauma (1 study, n=64), reported hospital length of stay (LOS) in days as median and interquartile range (IQR) or range. Analysis was therefore not possible. However, the original studies reported the difference in length of stay (trauma: median 1 fewer day in the BC treatment group, p=0.85 (ns), [14]; nontrauma: median 6 more days in the BC treatment group, p=0.02, [15]). (Figure s3.c)

**Mechanical ventilation (length of stay):** Three trials (n=231) reported mechanical ventilation, one trauma (n=107) and two non-trauma trials (n=124). Data could not be combined from all studies in a single meta-analysis due to presentation as median and interquartile range (IQR) or range. There was no evidence of an effect in two of the three studies (trauma, n=107; non-trauma, n=60), and evidence of effect in favour of WB (median 45 hours less using mechanical ventilation than the BC group) in one small non-trauma study (n=64, p=0.04, [15]) (see supplementary Figure s3.d).

One study of non-trauma patients (n=65) reported separately that duration of oxygen dependence in hours was significantly reduced (mean difference 5.9 fewer hours [95%CI -10.83, -0.99]) in the WB group compared to the blood component group (see supplementary information Figure s3.d)

**ICU/HDU (length of stay):** Four studies (n=296), one trauma (n=107) and three non-trauma (n=189), reported intensive care, critical care, or high dependency length of stay. Data could not be combined from all studies in a single meta-analysis due to presentation as median and interquartile range (IQR) or range by two of the four studies. There was no evidence of effect in these two studies (trauma, n=107; non-trauma, n=64). In the other two studies (non-trauma, 2 studies, n=125), there may be evidence of a reduction in length of stay with WB compared to BC (mean difference 7.1 fewer hours [95%CI -12.89, -1.31]), however, the difference was small, and there may not be a difference overall. (Figure s3.e).

**Infections:** There was no evidence of a difference in the number of patients experiencing infection in trauma and non-trauma patients (2 studies, n=171). The single trauma study (n=107) also separately reported incidence of sepsis, with a very low event rate in both groups, and no evidence of effect.

**Arterial thrombotic event:** A single study of trauma patients reported zero cases of arterial thrombotic events in both WB and BC groups (1 study, n=107).

**Transfusion reaction (febrile):** One study (N=294) in non-trauma patients reported no difference between treatment groups for febrile transfusion reaction, with very low event rate in both arms.

# DISCUSSION

## Summary of main results

The certainty of the evidence was GRADED as very low for all outcomes in this review. However, based on these studies , we saw no evidence of harm with WB transfusion versus blood components therapy (BC). There were some indications that WB therapy compared to BC therapy may be associated with shorter duration of oxygen dependence length of stay (LOS) (one small study in nontrauma, n=60, [19]), shorter ICU duration (based on analysable data from two trials, n=125, [16,19], and non-analysable data in one trial, n=64, [15], in the non-trauma subgroup), shorter hospital LOS and mechanical ventilation time (non-trauma, n=64, [15]).

For the remaining outcomes there were no differences between WB and BC therapy (wide CI, crossing line of no effect), though many of these outcomes were based on small single studies (very low certainty evidence).

## Overall completeness and applicability of the evidence

We attempted to identify all relevant studies by performing a comprehensive, systematic search of electronic and print resources. However, we did not include grey literature, such as conference proceedings, in the review.

## Quality of the evidence

The certainty of the evidence was GRADED as very-low for all outcomes. Downgrading was due to large imprecision (small sample size, and wide confidence intervals around the effect estimate), and serious risk of bias (unclear reporting in multiple domains, and high risk of bias in some studies for blinding, the randomisation process, and baseline imbalances).

## Potential biases in the review process

To our knowledge, our review process was free from bias. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured (including multiple databases), however, we did not search clinical trial registries. There were no restrictions for the language in which the paper was originally published. We pre-specified all outcomes and subgroups prior to analysis. There were insufficient numbers of included trials within the meta-analyses for us to use a funnel plot to examine the risk of publication bias.

As this is a rapid systematic review, we did not undertake duplicate screening, data extraction, or analysis. However, a second reviewer (SJB) verified all screening decisions made by the lead reviewer (LJG) (two reviewers excluded, and one reviewer included), and likewise checked and verified the data extraction and GRADE processes, as described by the Cochrane Interim Guidelines for Rapid Reviews [11]. Additionally, the clinicians

(LJE and LGr) were consulted for disagreements or need for clarification regarding inclusion of studies, and with decisions for appropriate meta-analysis of results.

**Agreements and disagreements with other studies or reviews**

The focus of this review was to evaluate the possible difference in "all-cause" harms to patients as a result of WB (both fresh and stored) transfusions in comparison to the use of BC in all clinical settings, and for any patients (paediatric and adults). We chose mortality (24-hour mortality, 30-day mortality) as our primary outcome, as we believe it is the most important potential harm of any intervention. Taking into consideration several limitations for the included trials (small sample size, risks of bias, very low certainty of evidence), from this review there was no evidence of benefit or harm with WB transfusion compared to BC therapy in trauma and non-trauma patients for 24-hour and 30-day mortality. Data for 30-day mortality showed a small difference in direction of effect by subgroup, where for trauma it favoured BC, for non-trauma it favoured WB therapy, though these effects were not significant. More importantly, in the trauma group, the data were based on one very small trial, which was underpowered to evaluate mortality as an outcome and had major baseline imbalances between the study groups of unsurvivable injury. Our results are consistent with the two previous systematic reviews in trauma [9,22], which have shown no evidence of benefit or harm with WB transfusion versus BC on overall mortality, and like us, have highlighted the need for larger trials in this setting.

The other outcomes showing potential harm to a patient that we were interested in were organ injury, transfusion related adverse events, and duration of hospital or ICU stay. Overall, we saw no difference between WB and BC in organ injury rates or transfusion-related adverse events (such as TRALI). However, the overall reporting of these outcomes was very poor for most studies, with only two studies reporting organ injury (one trauma, n=107, and one non-trauma, n=28), and no study reported on incidence of transfusion related anaphylaxis or allergy. A systematic review by Malkin and colleagues [22] also showed that in a trauma setting there was no evidence of increased transfusion related reactions with WB versus BC therapy, however, there was an increase in the organ failure rates (AKI and ARDS) with fresh WB transfusion, something we did not see in our review. The main reason for this discrepancy in results is likely to be because we included only RCTs in our review, whereas Malkin included both randomised and non-randomised controlled trials, as well as retrospective observational studies. Another systematic review that evaluated fresh WB
(defined as whole blood transfused within 24 hours of collection that has not been refrigerated for storage [2]) showed similar results with regards to survival rate and adverse events, however studies included in this review were all from military, whereas in

our review we included both civilian and military, fresh WB and non-fresh WB studies, and trauma and non-trauma studies.

For non-trauma settings, we are not aware of any other reviews that have compared the safety (using our broader definition of safety, not only transfusion-related complications) of WB versus BC therapy for management of bleeding, which is a strength of this review. Our results show that for other outcomes (LOS in hospital or ICU), there is no evidence that WB transfusion causes harm compared to BC, and there were some signals that WB therapy may be beneficial, though all included studies were underpowered to answer these outcomes. While results of this review may be reassuring for blood services and hospitals who are considering implementation of WB transfusion for treatment of major bleeding associated with trauma and non-trauma settings, we cannot emphasise enough the need for larger RCTs to validate these results.

## CONCLUSION

There appears to be little to no difference in safety (broader “all-cause” harms, not only transfusionrelated complications) between whole blood and blood component therapy, based on small studies with very low certainty of the evidence. There were some indications that WB therapy compared to BC therapy may be associated with shorter duration of oxygen dependence length of stay, shorter ICU duration and shorter stay in hospital. However, further large trials are still required to establish the overall safety of whole blood compared to blood component therapy in both trauma and non-trauma (surgery) patients.

## Contributions of authors

**Louise Geneen (LJG):** systematic reviewer and methodologist; developed and registered the protocol, screened all titles, full texts, and performed handsearching, extracted and quality appraised the data (risk of bias and GRADE), undertook analyses, wrote the manuscript of the review.

**Susan Brunskill (SJB):** systematic reviewer and methodologist; developed the protocol, screened all titles, verified full text exclusions, verified extracted data and risk of bias assessment, contributed to the development of manuscript.

**Carolyn Doree (CD):** information specialist; developed search strategy and performed all searches (including de-duplication), contributed to the development of the manuscript.

**Lise Estcourt (LJE):** clinical adviser and methodologist; developed the protocol, advised on appropriate pooling of data (meta-analysis), advised on clinical interpretation of the data, contributed to the development of the manuscript.

**Laura Green (LGr):** clinical lead for the review; conceived the idea for the review, developed the protocol, advised on clinical interpretation of the data, contributed to the development of the manuscript.

All authors contributed, read, and approved the review.

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Figure 1 – PRISMA flow diagram

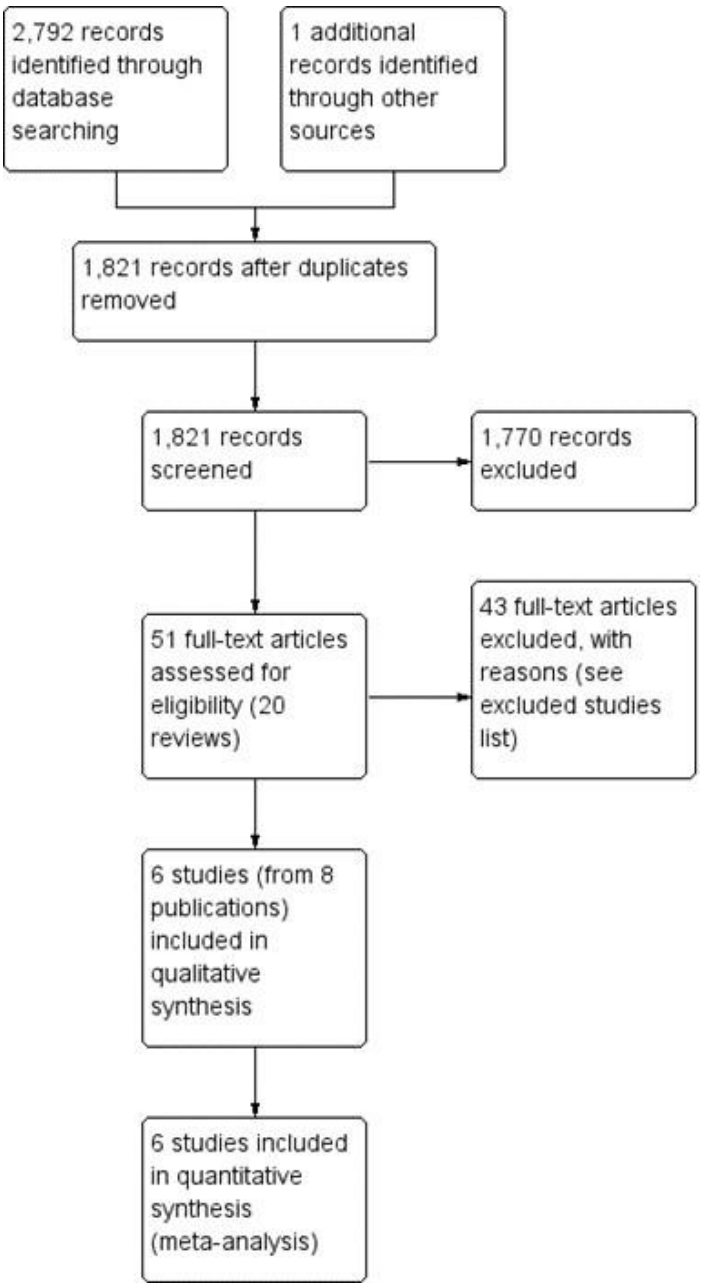
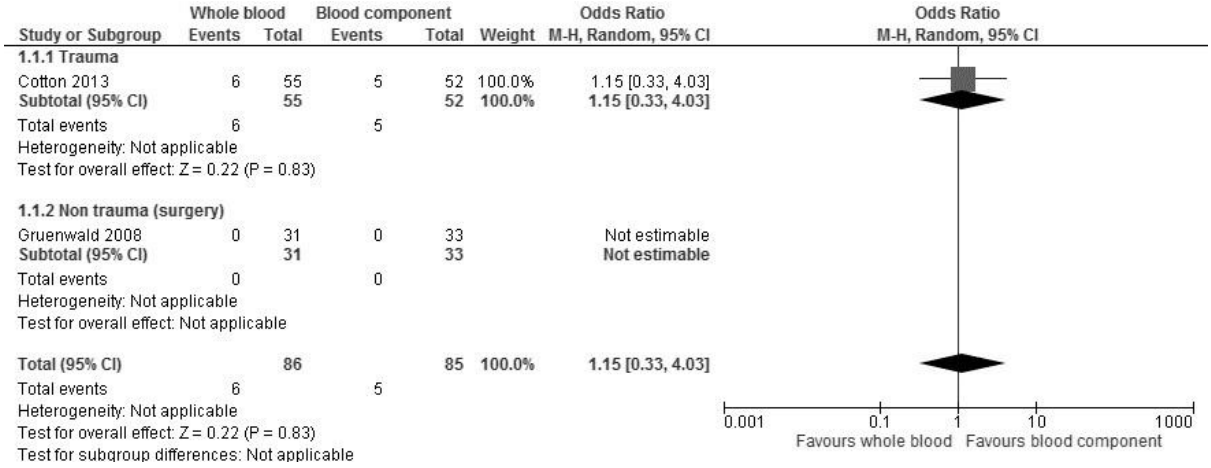
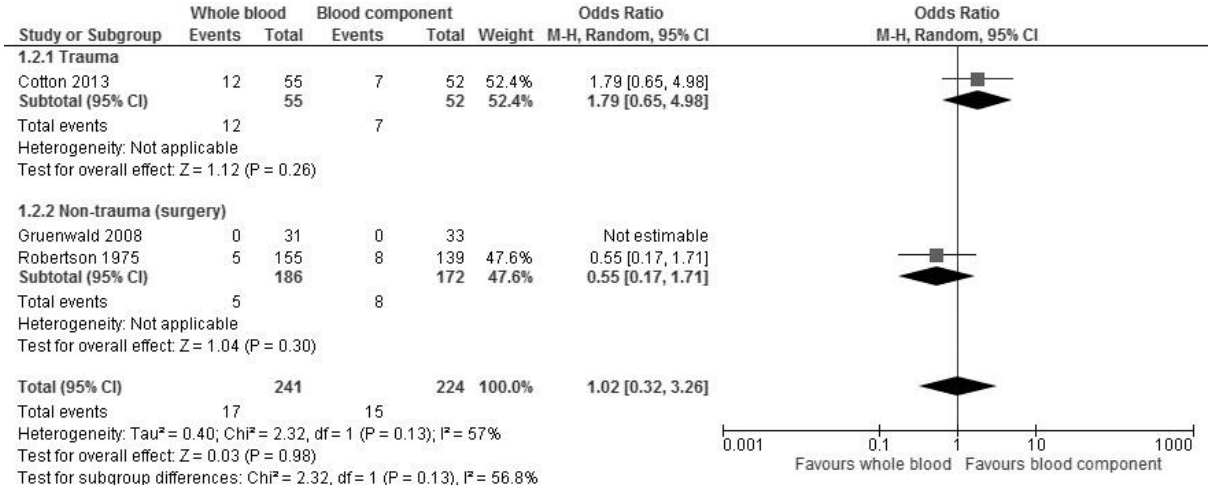


Figure 2 – Forest plots for primary outcome (24-hour and 30-day all-cause mortality)

24-hour all-cause mortality



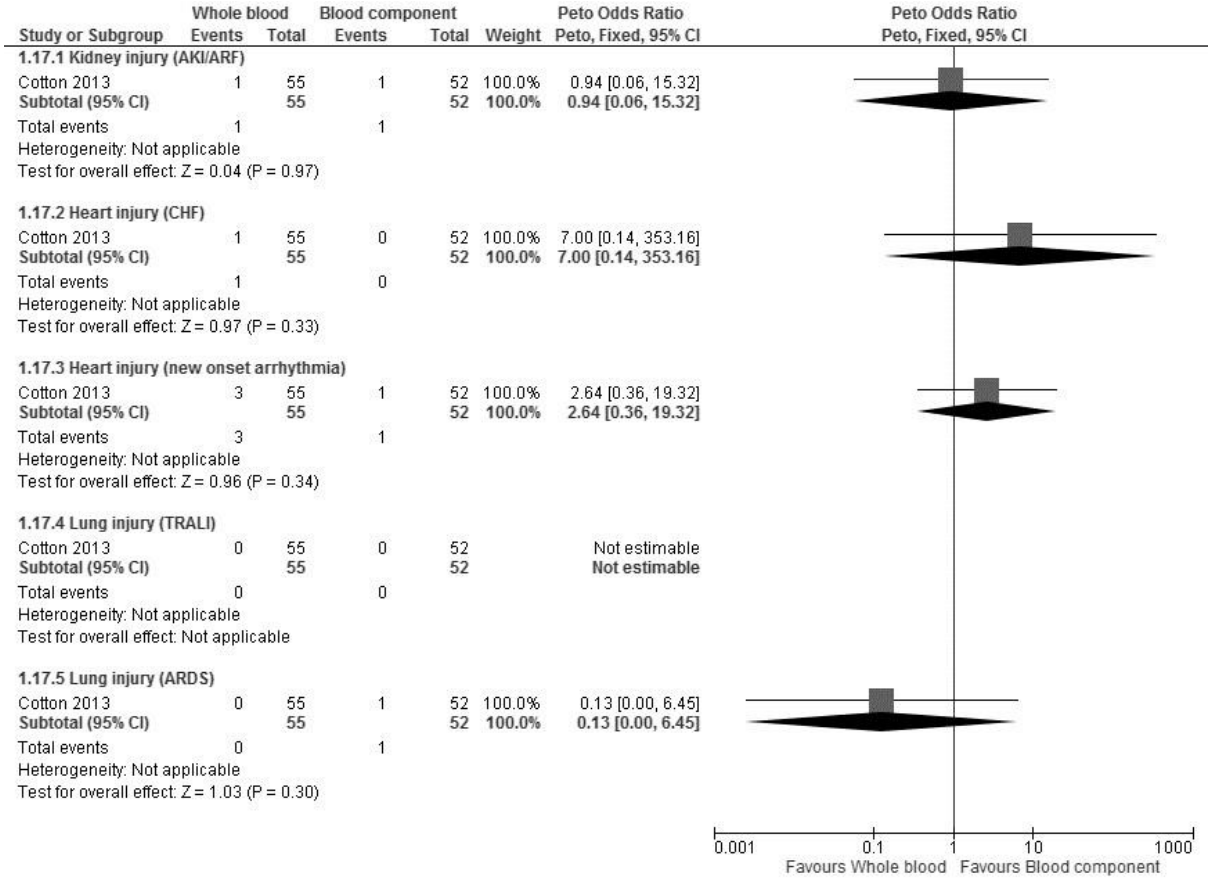

30-day all-cause mortality



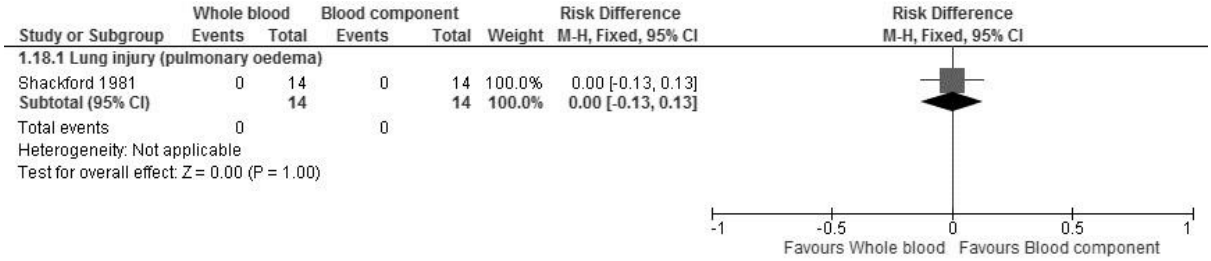

*Footnote: GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) for 24-hour and 30-day all-cause mortality (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 3 of the 5 non-trauma studies: Shackford 1981, Moritz 2000, Vasan 2021*

Figure 3 – Forest plots for secondary outcome (Organ injury for trauma and non-trauma patients)

Trauma patients




Non-trauma patients




*Footnote: GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) for Organ Injury (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 4 of the non-trauma studies: Robertson 1975, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

Table 1 – Study characteristics (in chronological order of publication)

| **Study details** | **Population inclusion criteria** | **Intervention**<br><br>**"whole blood"** | **Comparator**<br><br>**"blood component"** |
|---|---|---|---|
| **Robertson 1975** [17]<br><br>USA<br><br>Quasi-RCT | Non-trauma: any surgery (excludes CPB)<br><br>N=294 | "first 3 units received were whole blood" | "first 3 units were packed red cells" |
| **Shackford 1981** [18]<br><br>USA<br><br>RCT | Non-trauma: aortic surgery<br><br>N=28 | "whole blood" | "pRBCs … reconstituted with Ringer's lactate" |
| **Moritz 2000** [16]<br><br>Germany<br><br>RCT | Non-trauma: open heart surgery with CPB<br>N=60 | "fresh whole blood" | pRBC + FFP + platelets |
| **Gruenwald 2008** [15]<br><br>Canada<br><br>RCT (block randomisation) | Non-trauma: cardiac surgery with CPB (age <1 month) N=64 | reconstituted (leucocyte reduced) blood | stored blood components |
| **Cotton 2013** [14]<br><br>USA<br><br>RCT | Trauma: emergency: "highest-level trauma"<br><br>N=107<br><br>**baseline imbalance: TBI** | Leucocyte reduced WB | 1:1 (RBC:plasma) |
| **Vasan 2021** [19]<br><br>India<br><br>RCT | Non-trauma: spinal deformity surgery<br>N=65 | Fresh (leuco-reduced) WB | 1:1:1 (pRBC:FFP:platelets) |

*Abbreviations: RCT: randomised controlled trial; WB: whole blood; BC: blood component; pRBC: packed red blood cells; FFP: fresh frozen plasma; CPB: cardiopulmonary bypass*

Table 2 – Overview of results

| Outcome | Trauma (1 study) | Non-trauma (5 studies) | All participants (6 studies) | Comment |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| All-cause mortality | | | | |
| 24-hour | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ | 2 studies n=171 ⊕◯◯◯ | See Figure s3 a (i) |
| 30-day | 1 study n=107 ⊕◯◯◯ | 2 studies n=358 ⊕◯◯◯ | 3 studies n=465 ⊕◯◯◯ | $I^2$=57% (different direction of effect) See Figure s3 a (ii) |
| **Secondary outcomes** | | | | |
| Organ injury | | | | |
| Kidney injury | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (i) |
| Heart injury: CHF | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (ii) |
| Heart injury: arrhythmia | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (iii) |
| Lung injury: TRALI | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (iv) |
| Lung injury: ARDS | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (v) |
| Lung injury: pulmonary oedema | | 1 study n=28 ⊕◯◯◯ | | See Figure s3 b (vi) |
| Any other organ injury | | | | |
| Anaphylaxis/allergy | | | | |
| Hospitalisation LOS | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ ### | 2 studies n=171 ⊕◯◯◯ | presented as median (range), non-trauma study reports p=0.02 See Figure s3 c |
| Mechanical ventilation time | 1 study n=107 ⊕◯◯◯ | 2 studies n=124 ⊕◯◯◯ ++ | 3 studies n=231 ⊕◯◯◯ | could not combine data as presented as median (IQR or range) See Figure s3 d (i) |
| Oxygen dependence time | | 1 study n=64 ⊕◯◯◯ ### | | See Figure s3 d (ii) |
| ICU/HDU LOS | 1 study n=107 ⊕◯◯◯ | 3 studies n=189 ⊕◯◯◯ ++ | 4 studies n=296 ⊕◯◯◯ | could not combine data as presented as median (IQR or range) See Figure s3 e |
| Infections: any infection | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ | 2 studies n=171 ⊕◯◯◯ | See Figure s3 f (i) |
| Infections: Sepsis | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 f (ii) |
| Arterial thrombotic events (MI, stroke, cerebrovascular events) | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 g |
| Transfusion reaction | | 1 study n=294 ⊕◯◯◯ | | See Figure s3 h |

Most outcomes showed no evidence of effect. Grey shading indicates no data were available for this outcome in this group/subgroup.

### = evidence of effect (favouring whole blood); ++ = could not combine all data due to presentation as median and IQR/range, but some data are significant, others are non-significant (if combined unlikely to be significant)

⊕◯◯◯ = very low certainty of evidence; ⊕⊕◯◯ = low certainty of evidence; ⊕⊕⊕◯ = moderate certainty of evidence; ⊕⊕⊕⊕ = high certainty of evidence

**Supplementary information for a rapid systematic review and meta-analysis of whole blood compared to blood component therapy for acquired bleeding**

## Contents

## Search strategy

The following databases were searched for systematic reviews and randomised controlled trials on 2.3.21:
MEDLINE (Ovid, 1946 onwards)
PubMed (for epublications ahead of print only)
Embase (Ovid, 1974 onwards)
CENTRAL (*The Cochrane Library*, 2021 Issue 3)
Transfusion Evidence Library (Evidentia, 1950 onwards)

**SEARCH STRATEGIES MEDLINE**

1. (whole blood and (transfus* or resuscitat*)).mp.
2. (whole blood adj10 (exsanguin* or haemorrrhag* or hemorrhag* or bleed* or massive blood loss or code red)).mp.
3. ((whole blood or WB) adj3 (allogeneic or fresh or warm or stored or cold-stored or unit* or therapy)).mp.

4. WB transfusion*.mp.
5. 1 or 2 or 3 or 4
6. Meta-Analysis/ or Network Meta-Analysis/ 7. Systematic Review.pt.
8. "Systematic Reviews as Topic"/ or "Meta-Analysis as Topic"/ 9.
((meta analy* or metaanaly*) and (trials or studies)).ab.
10. (meta analy* or metaanaly* or evidence-based).ti.
11. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.
12. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
13. Cochrane Database of systematic reviews.jn.
14. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
15. ((electronic* or online) adj (sources or resources or databases)).ab.
16. network meta-analys*.tw,kf.
17. or/6-16
18. Review.pt.
19. Randomized Controlled Trials as Topic/ 20. selection criteria.ab. or critical appraisal.ti.
21. (data adj (abstraction or extraction or analys*)).ab.
22. exp Randomized Controlled Trial/
23. or/19-22
24. 18 and 23 25. 17 or 24
26. (Controlled Clinical Trial or Clinical Trial Protocol).pt.
27. exp Randomized Controlled Trial/ 28. (randomi* or randomly or placebo).tw,kf.
29. trial.ti,kf.
30. Clinical Trials as Topic/
31. Clinical Trial, Phase III/ or ("phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kf.
32. or/26-31
33. 25 or 32
34. (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/
35. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset* or chickens or hens).ti.

36. Editorial.pt.
37. 34 or 35 or 36
38. 33 not 37
39. 5 and 38

**PubMed**

#1 ((transfus* OR resuscitat*) AND "whole blood")
#2 ("whole blood" AND (exsanguin* OR haemorrrhag* OR hemorrhag* OR bleed* OR "massive blood loss" OR "code red"))
#3 ("fresh whole blood" OR "warm whole blood" OR "stored whole blood" OR "cold-stored whole blood" OR "whole blood units" OR "whole blood therapy")
#4 ("WB transfusion" OR "WB transfusions")
#5 #1 or #2 or #3 or #4
#6 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR “evidence synthesis” OR "literature search" OR medline OR pubmed OR cochrane OR embase)
#7 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#8 #5 AND #6 AND #7

**Embase**

1. "Fresh Whole Blood Transfusion"/
2. *Blood Transfusion/ and whole blood.tw,kw.
3. (whole blood adj10 (transfus* or resuscitat*)).tw,kw.
4. (whole blood adj10 (exsanguin* or haemorrrhag* or hemorrhag* or bleed* or massive blood loss or code red)).tw,kw.
5. ((whole blood or WB) adj3 (allogeneic or fresh or warm or stored or cold-stored or unit* or component* or therapy)).tw,kw.
6. WB transfusion*.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Meta Analysis/
9. (meta analy* or metaanaly*).ti,kw.
10. ((meta analy* or metaanaly*) and (trials or studies)).ab.
11. Systematic Review/
12. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kw.
13. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or google scholar or google database or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
14. ((electronic* or online) adj (sources or resources or databases)).ab.
15. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
16. exp "Controlled Clinical Trial (Topic)"/
17. or/8-16 18. Review.pt.
19. (data extraction or selection criteria).ab.
20. 18 and 19 21. 17 or 20
22. Editorial.pt.
23. 21 not 22

24. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ 25. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.
26. 23 or 24 or 25
27. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset* or chickens or hens).ti. and animal experiment/
28. Animal experiment/ not (human experiment/ or human/)
29. (exp animal/ or nonhuman/) not exp human/
30. 27 or 28 or 29
31. 26 not 30
32. limit 31 to (conference abstracts or embase)
33. 7 and 32

**CENTRAL**

#1 ((transfus* OR resuscitat*) AND "whole blood"):ti,ab
#2 ("whole blood" near/6 (exsanguin* or haemorrrhag* or hemorrhag* or bleed* or "blood loss" or "code red")):ti,ab
#3 ("whole blood" near/2 (fresh or warm or stored or cold-stored or unit* or therapy or group)):ti,ab
#4 ("WB transfusion" or "WB transfusions"):ti,ab
#5 MeSH descriptor: [Blood Transfusion] this term only
#6 "whole blood"
#7 #5 and #6
#8 #1 or #2 or #3 or #4 or #7

**TRANSFUSION EVIDENCE LIBRARY**

Search term: "whole blood"

## Figures

Figure s1 – Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

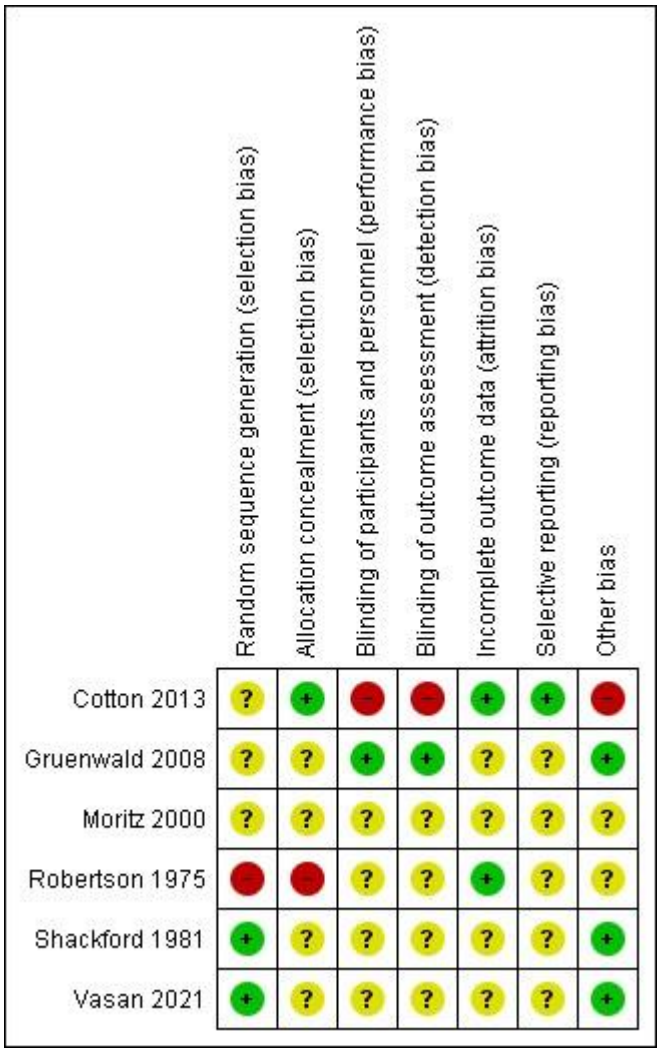


Figure s2 – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

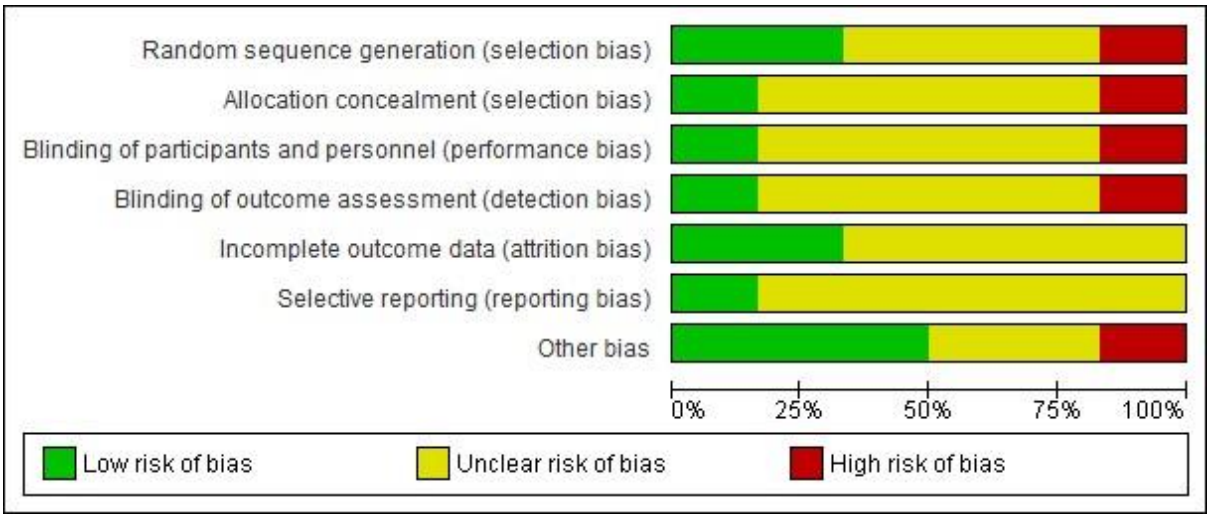
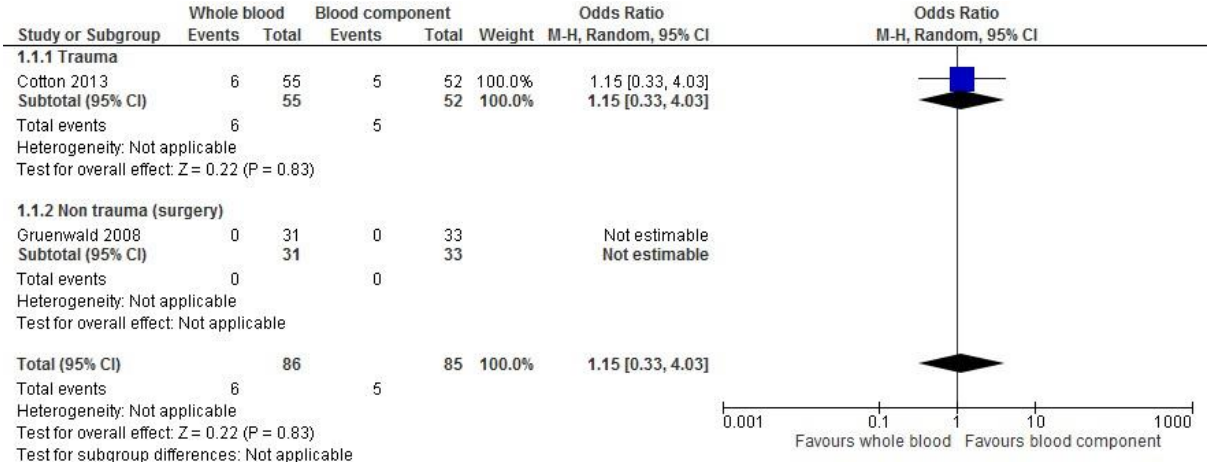


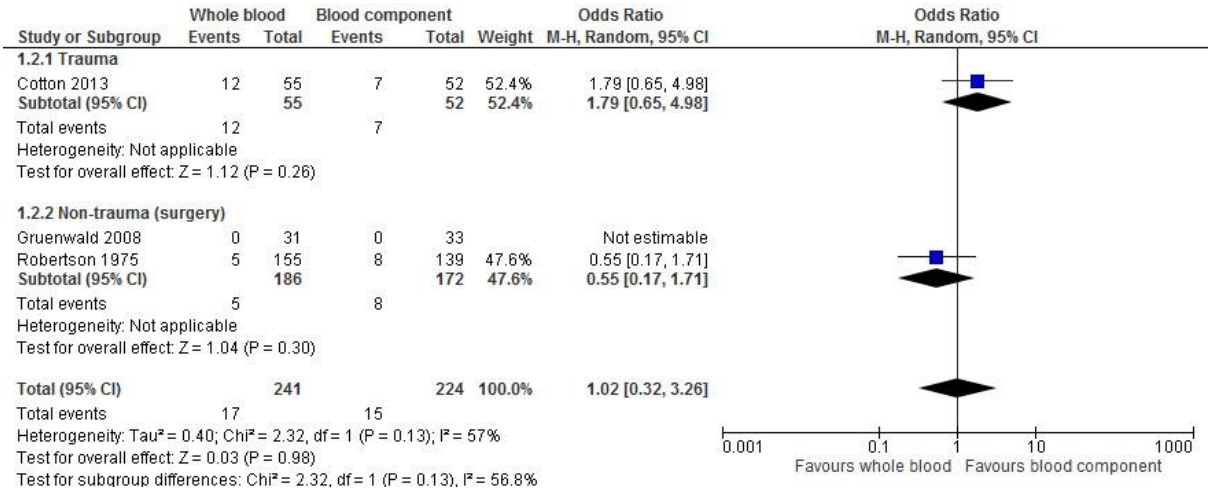
Figure s3 – Forest plots and analyses of all outcomes

*Figure s3 a (i): 24-hour mortality*



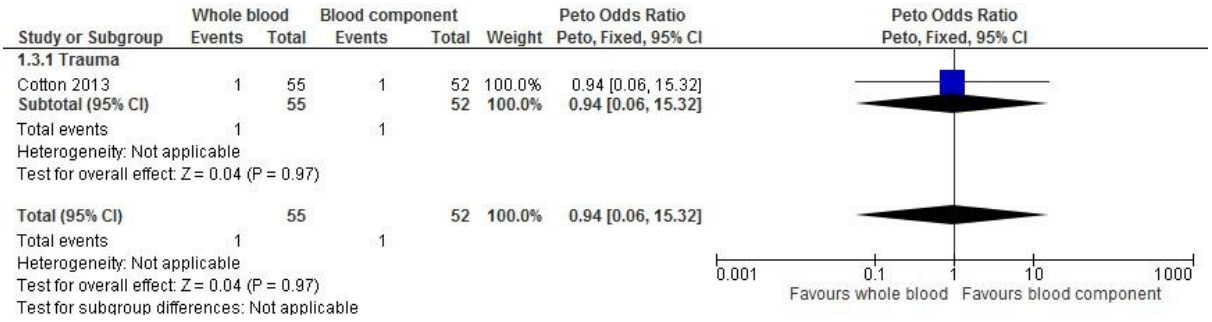

*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 4 studies: Robertson 1975, Shackford 1981, Moritz 2000, Vasan 2021*

*Figure s3 a(ii): 30-day mortality*




*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 3 studies: Shackford 1981, Moritz 2000, Vasan 2021*

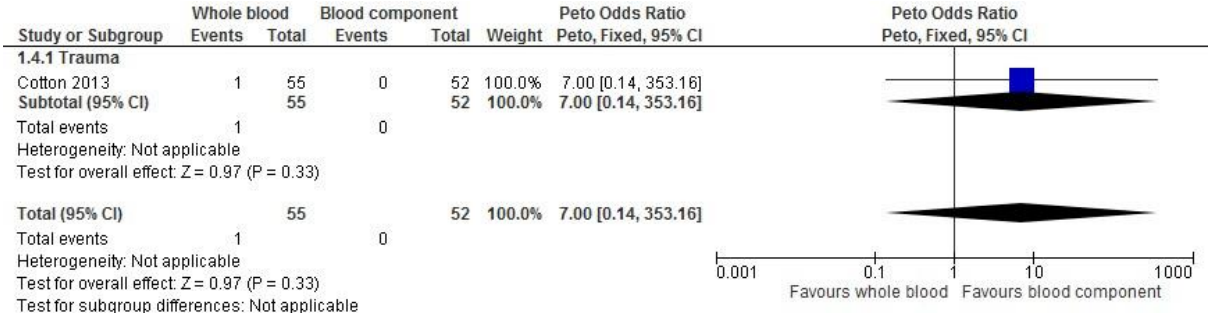
Figure s3 b (i) Organ injury: Kidney injury (AKI/ARF)




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

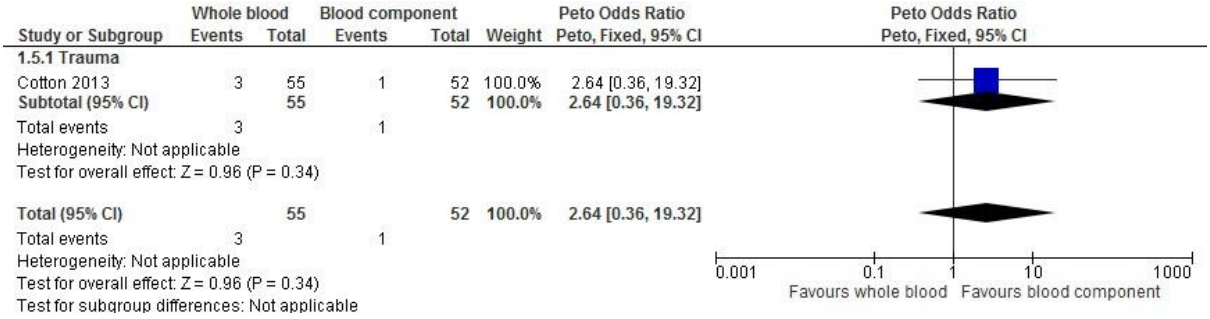
*Figure s3 b (ii) Organ injury: Heart injury (CHF)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

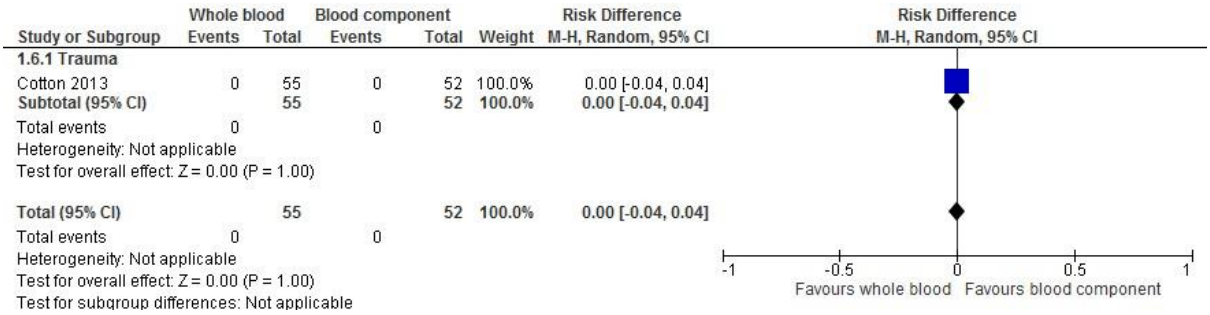
*Figure s3 b (iii) Organ injury : Heart injury (New onset arrhythmia)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

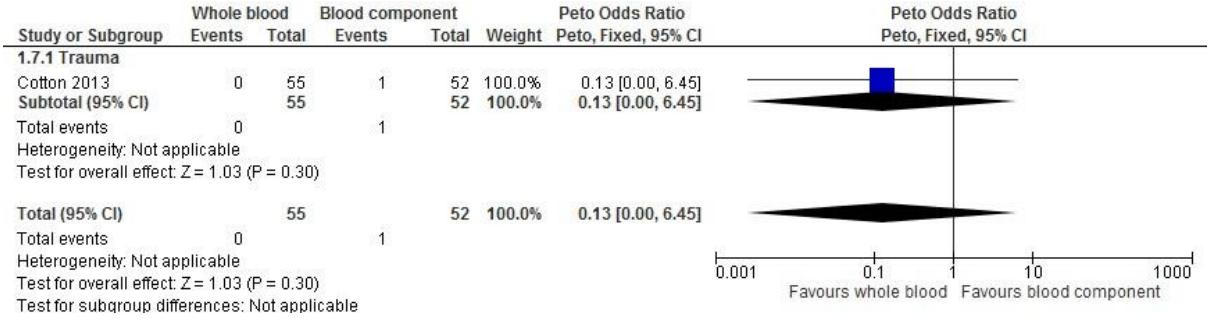
*Figure s3 b (iv) Organ injury: Lung injury (TRALI)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

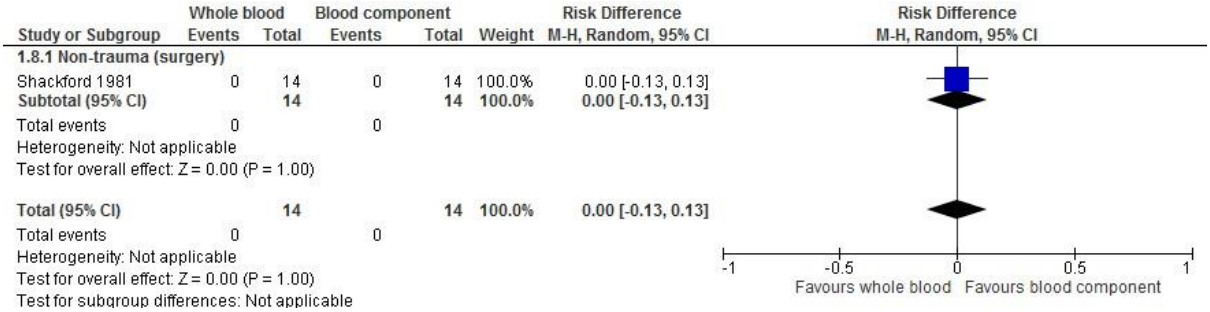
*Figure s3 b (v) Organ injury: Lung injury (ARDS)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure; TRALI: transfusion related acute lung injury*

*Figure s3 b (vi) Organ injury: Lung injury (pulmonary oedema)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Moritz 2000, Gruenwald 2008, Cotton 2013, Vasan 2021*

*Abbreviations: AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CHF: congestive heart failure;*

*TRALI: transfusion related acute lung injury*

*Figure s3 c: Hospital LOS (days)*

| | Whole blood | Blood component |
|---|---|---|
| Trauma: Cotton 2013 | Median 15 (IQR 7-28) days [n=55] | Median 14 (IQR 7-23) days [n=52] |
| Non-trauma: Gruenwald 2008 | Median 12 (range 6-36) days [n=31] | Median 18 (range 7-79) days [n=33] |

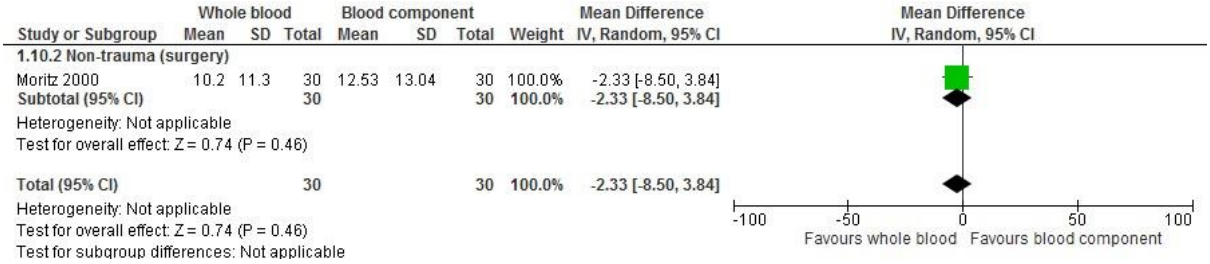
*Presented as median IQR/range only; Trauma: Cotton 2013; Non-trauma: Gruenwald 2008*

*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 4 studies: Robertson 1975, Shackford 1981, Moritz 2000, Vasan 2021*

*Meta-analysis was not possible due to data presentation as median and IQR/range only Abbreviations:*

*LOS: length of stay; IQR: interquartile range*

*Figure s3 d (i): Mechanical ventilation LOS (reported as days or hours)*




*Moritz 2000 reported and analysed as mean and SD in hours*

| | Whole blood | Blood component |
|---|---|---|
| Trauma: Cotton 2013 | Median 0 (IQR 0-4) days [n=55] | Median 0 (IQR 0-4) days [n=52] |
| Non-trauma: Gruenwald 2008 | Median 4.96 (range 1.17-20) days [n=31] | Median 6.83 (range 2.25-38) days [n=33] |

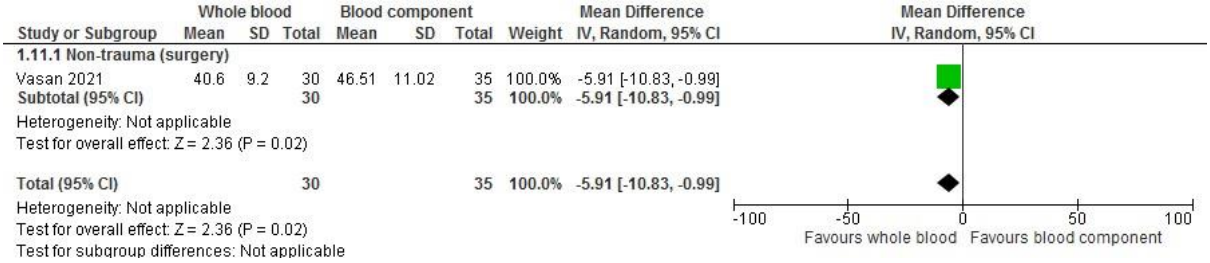
*Presented as median IQR/range only; Trauma: Cotton 2013; Non-trauma: Gruenwald 2008 (converted from hours to days)*

*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 3 studies: Robertson 1975, Shackford 1981, Vasan 2021*

*Meta-analysis of all studies was not possible due to presentation as median and IQR/range for some data. Abbreviations:*

*LOS: length of stay; IQR: interquartile range*

*Figure s3 d (ii): Oxygen dependence LOS (hours)*

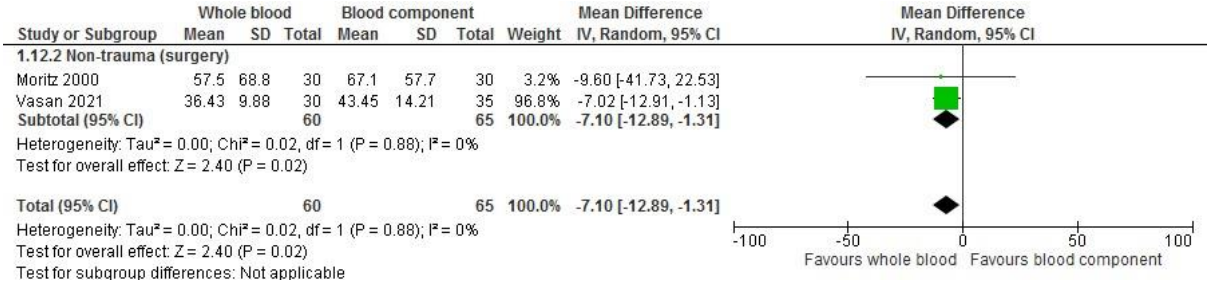



*Vasan 2021 reported and analysed as mean and SD in hours*

*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Cotton 2013*

*Abbreviations: LOS: length of stay; IQR: interquartile range*

*Figure s3 e.: ICU/ITU/HDU LOS (reported as days or hours)*




*Moritz 2000 and Vasan 2021 reported and analysed as mean and SD in hours*

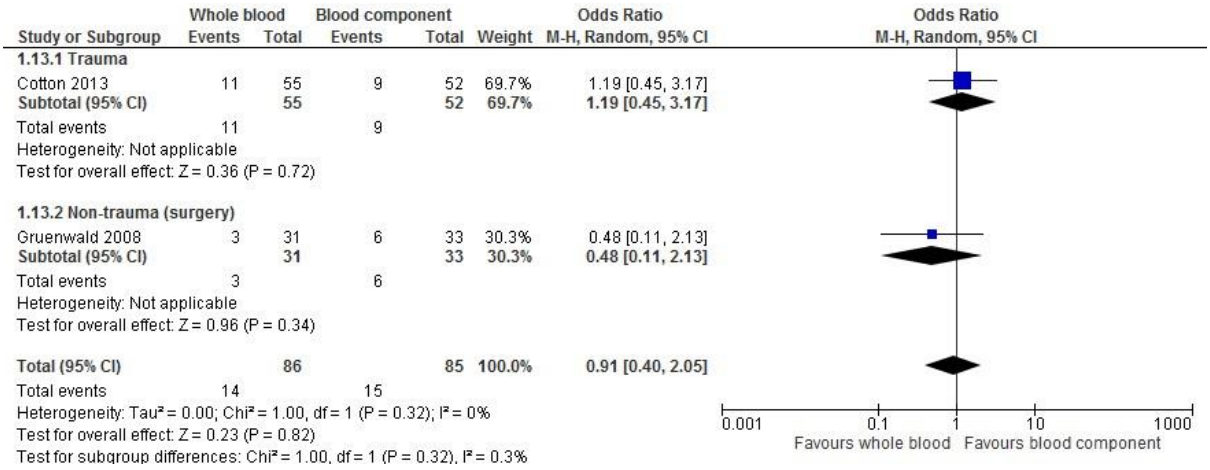
| | Whole blood | Blood component |
|---|---|---|
| Trauma: Cotton 2013 | Median 0 (IQR 0-19) days [n=55] | Median 1 (IQR 0-13) days [n=52] |
| Non-trauma: Gruenwald 2008 | Median 5 (range 3-20) days [n=31] | Median 7 (range 1-39) days [n=33] |

*Presented as median IQR/range in days only; Trauma: Cotton 2013; Non-trauma: Gruenwald 2008*

*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 2 studies: Robertson 1975, Shackford 1981*

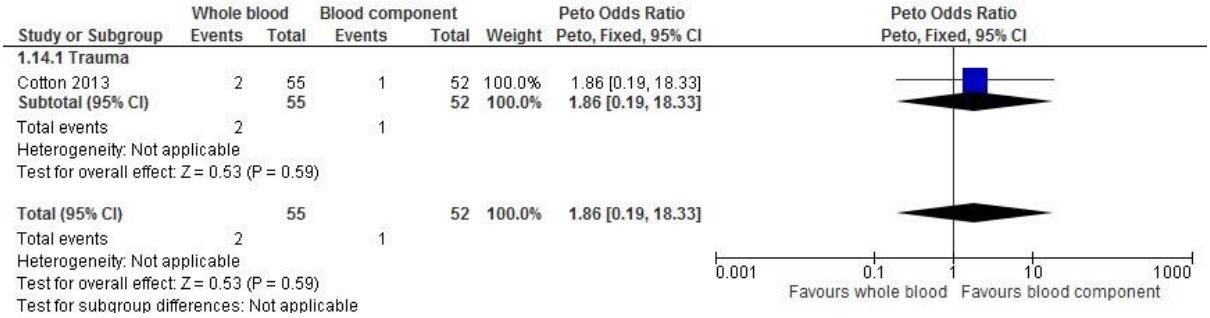
*Abbreviations: LOS: length of stay; IQR: interquartile range; ICU: intensive care unit; ITU: intensive therapy unit; HDU: high dependency unit*

*Figure s3 f (i): Infections*



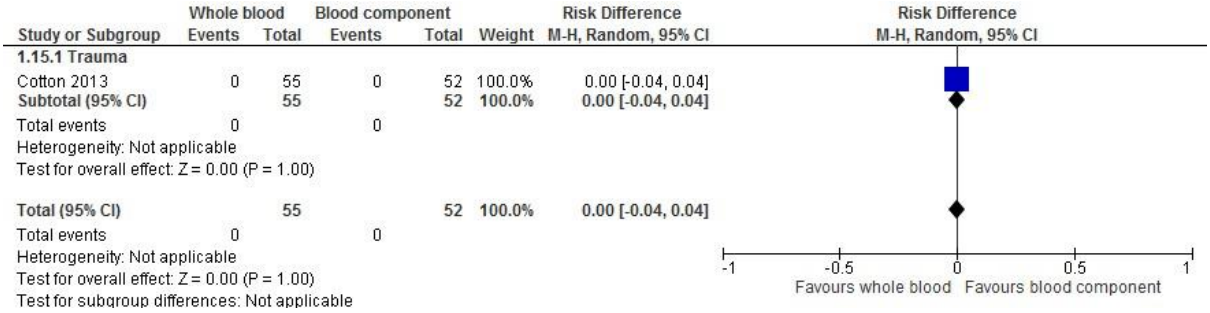

*GRADED as very-low quality (certainty of) evidence overall and for each subgroup (trauma and non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 4 studies: Robertson 1975, Shackford 1981, Moritz 2000, Vasan 2021*

*Figure s3 f (ii): Sepsis*



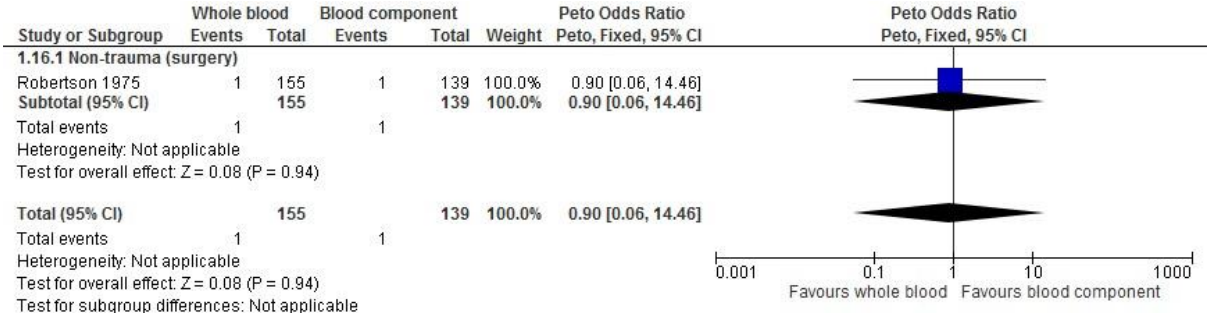

*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Figure s3 g: Arterial/thrombotic event (myocardial infarction, stroke, cerebrovascular events)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Robertson 1975, Shackford 1981, Moritz 2000, Gruenwald 2008, Vasan 2021*

*Figure s3 h: Transfusion reaction (febrile)*




*GRADED as very-low quality (certainty of) evidence overall and for only subgroup reported (non-trauma) (see Supplementary Table s6 – GRADE assessment). Outcome was not reported by 5 studies: Shackford 1981, Moritz 2000, Gruenwald 2008, Cotton 2013, Vasan 2021*

## Tables

Table s1 – excluded studies and reasons

| Reference | Reason for exclusion |
|---|---|
| Avery 2020 [1] | SR - references checked, no additional studies from included studies, only one RCT included (Cotton 2013) already in our included list. Excluded study list not provided |
| Bahr 2020 [2] | Narrative review - references checked, only one RCT mentioned (Cotton 2013) |
| Blair 1986 [3] | Intervention - unclear if whole blood was used: acute severe GI haemorrhage treated with "at least 2 units of blood or no blood" |
| Crowe 2020 [4] | SR - references checked, no additional studies from included studies, only one RCT (Cotton 2013) already in included list. Excluded study list not provided |
| Crowe 2020 [5] | Conference abstract of SR only - no references available to check |
| Cruciani 2021 [6] | SR - references checked, no additional studies from included studies, two reports of one RCT (Cotton 2013; Rahbar 2015) already included. Excluded study list not provided. |
| Dretzke 2014 [7] | SR protocol only - cannot locate full SR |
| Ezz El Arab 2002 [8] | Unavailable from British Library and all available resources. No abstract or full text |
| Foster Jr 1988 [9] | Retrospective analyses of cancer deaths that received blood transfusion (whole blood or packed cells) compared to no blood transfusion |
| Ghaemi 2012 [10] | Population - no major bleed (ABO haemolytic disease only)<br>Comparison - component (O packed cells) vs component (infant isogroup) |
| Green 2018 [11] | Conference abstract of trial protocol only - no references available to check. Observational trial (no randomisation) |
| Gurusamy 2011 [12] | Non-relevant SR - no additional studies; one trial examined whole blood vs blood components (Laine 2003 - no relevant outcomes for this review) |
| Hershey 1992 [13] | Narrative review - references checked, no studies of relevance |
| Hertfelder 1992 [14] | Conference abstract only - no mention of randomisation |
| Hertfelder 1992 [15] | Conference abstract only - no mention of randomisation |
| Jensen 1992 [16] | Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only |
| Jensen 1993 [17] | Same trial as Jensen 1992, no additional data in this abstract (full text unavailable from British Library and all available resources) |
| Jensen 1995 [18] | Jensen 1992 cohort - Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only |
| Jensen 1996 [19] | Jensen 1992 cohort - Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only |
| Jones 2016 [20] | SR of blood components of different ratios. No relevant references. Unable to access excluded study list |
| Kallos 1974 [21] | No outcomes of interest for this review |
| Kohli 2019 [22] | SR of guidelines regarding transfusion practice (only relevant guideline is obstetric bleeding), and scoping review of trials comparing whole blood or packed red cells - references checked, no relevant references. Excluded study list not provided |
| Kohli 2017 [23] | Conference abstract of SR only - no references available to check |
| Laine 2003 [24] | No outcomes of interest for this review |
| Larsen 2017 [25] | SR of coagulation ability - references checked, no relevant references. Excluded study list not provided |
| Lavee 1989 [26] | No outcomes of interest for this review |
| Maitland 2020 [27] | Conference abstract only.<br>Population - severe anaemia (<6g/dL), unclear as to whether major bleed is cause (unlikely) |
| Malkin 2021 [28] | SR - references checked; no additional studies (only RCT included Cotton 2013); excluded study list not provided |

| Reference | Reason for exclusion |
|---|---|
| Manno 1991 [29] | No outcomes of interest for this review |
| Martinaud 2019 [30] | RCT protocol; ongoing study- T STORHM study, not yet recruiting |
| McGrath 2016 [31] | Narrative review - all references checked; no additional relevant references |
| McQuilten 2018 [32] | SR - references checked, only one relevant RCT listed - already in our list of full text assessment (Cotton 2013). Excluded study list not provided. |
| Miller 1975 [33] | No randomisation |
| Mohr 1988 [34] | Conference abstract of RCT only - unclear comparison (appears to be component vs component, then both groups received remaining component to total whole blood in but in different component order); unable to extract data |
| Mohr 1988 [35] | No outcomes of interest for this review |
| Moritz 2000 [36] | Duplicate |
| Mou 2004 [37] | Population not treated for major bleed (blood used in cardiopulmonary bypass circuit/pump only during surgery) |
| Naumann 2020 [38] | SR - references checked; all observational. Unable to access excluded study list to check non-trauma studies |
| Seheult 2019 [39] | Narrative review - references checked; no relevant completed studies listed. Two ongoing trials listed (PPOWER and STORHM) |
| Spinella 2016 [40] | Narrative review - references checked; no additional studies |
| Vamvakas 2002 [41] | SR - references checked (no additional references). Excluded studies also checked |
| Walsh 2020 [42] | Narrative review - all references checked; only on RCT mentioned (Cotton 2013), no additional relevant references.<br>Mentions three ongoing trials (SWAT [observational], PPOWER [RCT, finished Oct 2020], STORHM [RCT, not yet recruiting]) |
| Walsh 2021 [43] | Narrative review - references checked. Only one RCT listed (Cotton 2013) and 3 ongoing trials (STORHM [RCT, not yet recruiting], PPOWER [RCT, finished Oct 2020], SWAT [observational]) |

Table s2 - Studies excluded due to lack of relevant outcomes, or incorrect comparison

| Reference | Reason for exclusion and relevant outcomes for future review |
|---|---|
| Jensen 1992 [16] | Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only |
| Jensen 1993 [17] | Jensen 1992 cohort - Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only. |
| Jensen 1995 [18] | Jensen 1992 cohort - Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only |
| Jensen 1996 [19] | Jensen 1992 cohort - Compares unfiltered whole blood with filtered (leucocyte reduced) whole blood, not compared to blood components only. |
| Kallos 1974 [21] | No outcomes of interest for this review.<br>**Outcomes:** Blood loss |
| Laine 2003 [24] | No outcomes of interest for this review.<br>**Outcomes**: Blood requirement |
| Lavee 1989 [24] | No outcomes of interest for this review.<br>**Outcomes:** re-operation |
| Manno 1991 [29] | No outcomes of interest for this review.<br>**Outcomes**: Blood loss |
| Mohr 1988 [35] | No outcomes of interest for this review.<br>**Outcomes**: Re-operations, Blood loss (24hr), Blood requirement, Bleeding time |

Table s3 - ongoing studies

| | | | |
|---|---|---|---|
| **T-STORHM.**<br>*Evaluation of a Transfusion Therapy Using Whole Blood in the Management of Coagulopathy in Patients with Acute Traumatic Haemorrhage* | RCT<br>France<br><br>ClinicalTrials.gov Identifier: NCT04431999 | Whole blood *versus* Fractionated blood products | Primary outcome:<br>Non inferiority on the correction of coagulopathy using whole blood compared to the use of component therapy<br><br>*Not yet recruiting* |
| **PPOWER.**<br>*Pragmatic Prehospital Group O Whole Blood Early Resuscitation Trial* | RCT<br>USA<br><br>ClinicalTrials.gov Identifier: NCT03477006 | Whole blood *versus* Standard Care: component (1:1:1) trauma resuscitation | Primary outcome:<br>28-day all-cause mortality<br><br>*Completed Oct 2020, no results posted* |
| **SWAT**<br>*Shock, Whole Blood, and Assessment of TBI S.W.A.T. (LITES TO 2)* | Observational<br>USA<br><br>ClinicalTrials.gov Identifier: NCT03402035 | Whole blood *versus* Component therapy | Primary outcome:<br>4-hour mortality<br><br>*Recruiting* |

Table s4 - study characteristics of included studies (in chronological order)

| Study details | Population inclusion criteria | Intervention "whole blood" | Comparator "blood component" | Standard care (both groups) | Outcomes relevant to this review |
|---|---|---|---|---|---|
| **Robertson 1975** [44]<br><br>USA<br><br>Quasi-RCT<br><br>N=294 | Non-trauma: any surgery (excl. CPB)<br><br>"all elective general, thoracic, and gynecologic operations, excluding only CPB procedures" | "first 3 units received were whole blood" | "first 3 units were packed red cells: red cells were "packed" by centrifugation followed by mechanical squeezing to separate plasma and RBCs." | "Units of blood in excess of those customarily prepared for a given procedure were not set up for the packed cell group, and plasma products were not given in conjunction with the packed red cells" | • In-hospital mortality<br>• Febrile blood transfusion reaction |
| **Shackford 1981** [45]<br><br>USA<br><br>RCT<br><br>N=28 | Non-trauma: aortic surgery | "whole blood in transfusion to replace intraoperative blood loss" | "pRBCs which were reconstituted with Ringer's lactate" | "Additional Ringer's lactate was given to patients in both groups during and after operation, to maintain a constant preload (PCWP within 2 torr of preoperative value) ... After operation, all patients were transferred ... and underwent ventilation with a Bennett MA-1 volume cycled ventilator, using the intermittent mandatory ventilation mode." | • Pulmonary oedema |
| **Moritz 2000** [36]<br><br>Germany<br><br>RCT<br><br>N=60 | Non-trauma: open heart surgery with CPB | "fresh whole blood" | pRBC + FFP + platelets | NR | • Intubation time<br>• ICU time |
| **Gruenwald 2008** [46]<br><br>Canada<br><br>RCT (block randomisation)<br><br>N=64 | Non-trauma: cardiac surgery with CPB<br><br>"Aged less than 1 month of age and scheduled for elective cardiac surgery requiring CPB" | reconstituted (leucocyte reduced) blood<br><br>"designated 2 units of ABO-compatible single random donor blood from two separate donors..., one of the RFWB units was prepared by reconstituting the components from the single donor that had been processed. The second unit of RFWB was prepared and released as required. All RFWB units were collected 2 days before the morning of the operation.<br><br>*CPB management*: Treatment group received RFWB for hemostasis and volume replacement as required until | stored blood components<br><br>"ABO-compatible stored blood components as per standard hospital protocol. Platelet components ... were random single donor platelets collected 2 to 5 days (median 4 days) before surgery that were either in their original state or further concentrated at the discretion of the attending anesthesiologist.<br><br>*CPB management*: 1 unit of FFP sulfate (2 IU/mL) added before aortic crossclamp removal. After CPB, control patients were given components for volume replacement<br>according to the ... transfusion guidelines." | All patients underwent modified ultrafiltration after CPB.<br><br>PRBCs and platelets were irradiated on the morning of the operation, before either reconstitution or release as individual components, depending on the randomization.<br><br>*CPB transfusion guidelines*: PRBC when the hematocrit value was less than 28% (acyanotic patients) or 32% (cyanotic patients), platelets (1 U/6 kg)when the platelet count was less than 100,000/mm3, cryoprecipitate if the fibrinogen level was less than 1.0 g/L, and additional FFP for ongoing bleeding | • 24-hour mortality<br>• 30-day mortality<br>• Hospital LOS<br>• Ventilation time<br>• CCCU time<br>• Post-op infections |

| Study details | Population inclusion criteria | Intervention "whole blood" | Comparator "blood component" | Standard care (both groups) | Outcomes relevant to this review |
|---|---|---|---|---|---|
| | | both available units were used, after which standard blood component therapy was used according to the ... transfusion guidelines" | | | |
| **Cotton 2013** [47]<br><br>USA<br><br>RCT<br><br>N=107 | Trauma: emergency<br><br>"met highest-level trauma activation criteria"<br><br>**baseline imbalance: unsurvivable TBI numbers higher in WB group**<br><br>*mWB: modified whole blood* | Leucocyte reduced WB<br><br>"mWB (1 U mWB): WB units were kept at 1 to 6◦C for up to 5 days also making the platelets non-functional via gross aggregation. Therefore, every 6 units of WB (as with every 6 units of RBC and plasma) were supplemented with 1 dose of apheresis platelets.<br>All units of blood were typed, crossmatched and leuco-reduced" | 1:1 (RBC:plasma)<br><br>1 U RBC+ 1 U plasma; RBC+plasma+aPLT for every 6 units | Each group also received 1 U platelets (apheresis or pre-pooled random donor) for every 6 U of mWB or 6 U of RBC + 6 U plasma. All units of blood for each study group were typed and crossmatched, leuco-reduced, and underwent standard infectious disease testing. | • 24-hour mortality<br>• 30-day mortality<br>• AKI/Acute renal failure<br>• CHF<br>• Arrythmia<br>• TRALI<br>• ARDS<br>• Hospital-free days<br>• Ventilator-free days<br>• ICU-free days<br>• Infectious complications<br>• Sepsis<br>• Myocardial infarction<br>• Stroke<br>• Cerebrovascular event |
| **Vasan 2021** [48]<br><br>India<br><br>RCT<br><br>N=65 | Non-trauma: spinal deformity surgery<br><br>"Patients ≤ 18 years of age undergoing corrective surgery for scoliosis and kyphosis involving vertebral fusion ≥ 6 levels and expected blood loss (BL) ≥ 750 ml" | "Fresh (leuco-reduced) WB was utilized within 24 h of collection." | 1:1:1 (pRBC:FFP:platelets)<br><br>"Components were separated by centrifugation and stored in a bag containing SAGM-2 (sodium chloride, adenine, dextrose, and mannitol). Components were always transfused in an equivalent ratio of 1:1:1 (pRBC:FFP:platelets)." | "All blood products were acquired from a random donor pool and utilized after stringent screening for infections in an in-house Government- approved blood bank facility. ... Blood bag CPD/SAGM-2 with inline leukocyte filter for WB (TERUMO PENPOL) was used for blood collection from donors. Leuco-reduction was then carried out by an inline leuco-filter with gravity-assisted transfer at 90 cm height. The second collection bag contained 63 ml of CPD solution (citric acid monohydrate, sodium citrate dehydrate, sodium dihydrogen phosphate dehydrate, and dextrose anhydrous) as anticoagulant.<br>All patients undergoing major SDS at our hospital are shifted to a high dependency unit | • Oxygen dependence<br>• HDU stay |

| Study details | Population inclusion criteria | Intervention "whole blood" | Comparator "blood component" | Standard care (both groups) | Outcomes relevant to this review |
|---|---|---|---|---|---|
| | | | | (HDU) postoperatively. All patients were started on intravenous fluids on postoperative days (POD) 0 and commenced on oral fluids on POD1 after the return of bowel sounds." | |

*Abbreviations: CPB: cardiopulmonary bypass; FFP: fresh frozen plasma; NR: nor reported; pRBC: packed red blood cells; RCT: randomised controlled trial; HDU: high dependency unit; LOS: length of stay; CCCU: cardiac critical care unit; ICU: intensive care unit; WB: whole blood*

Table s5 – overview of results

| Outcome | Trauma (1 study) | Non-trauma (5 studies) | All participants (6 studies) | Comment |
|---|---|---|---|---|
| Primary outcomes | | | | |
| All-cause mortality | | | | |
| 24-hour | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ | 2 studies n=171 ⊕◯◯◯ | See Figure s3 a (i) |
| 30-day | 1 study n=107 ⊕◯◯◯ | 2 studies n=358 ⊕◯◯◯ | 3 studies n=465 ⊕◯◯◯ | $I^2$=57% (different direction of effect) See Figure s3 a (ii) |
| Secondary outcomes | | | | |
| Organ injury | | | | |
| Kidney injury | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (i) |
| Heart injury: CHF | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (ii) |
| Heart injury: arrhythmia | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (iii) |
| Lung injury: TRALI | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (iv) |
| Lung injury: ARDS | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 b (v) |
| Lung injury: pulmonary oedema | | 1 study n=28 ⊕◯◯◯ | | See Figure s3 b (vi) |
| Any other organ injury | | | | |
| Anaphylaxis/allergy | | | | |
| Hospitalisation LOS | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ | 2 studies n=171 ⊕◯◯◯ | presented as median (range), non-trauma study reports p=0.02 See Figure s3 c |
| Mechanical ventilation time | 1 study n=107 ⊕◯◯◯ | 2 studies n=124 ⊕◯◯◯ | 3 studies n=231 ⊕◯◯◯ | could not combine data as presented as median (IQR or range) See Figure s3 d (i) |
| Oxygen dependence time | | 1 study n=64 ⊕◯◯◯ | | See Figure s3 d (ii) |
| ICU/HDU LOS | 1 study n=107 ⊕◯◯◯ | 3 studies n=189 ⊕◯◯◯ | 4 studies n=296 ⊕◯◯◯ | could not combine data as presented as median (IQR or range) See Figure s3 e |
| Infections: any infection | 1 study n=107 ⊕◯◯◯ | 1 study n=64 ⊕◯◯◯ | 2 studies n=171 ⊕◯◯◯ | See Figure s3 f (i) |
| Infections: Sepsis | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 f (ii) |
| Arterial thrombotic events (MI, stroke, cerebrovascular events) | 1 study n=107 ⊕◯◯◯ | | | See Figure s3 g |
| Transfusion reaction | | 1 study n=294 ⊕◯◯◯ | | See Figure s3 h |

Green = evidence of effect (favouring whole blood); orange = could not combine all data due to presentation as median and IQR/range, but some data are significant, others are non-significant (if combined unlikely to be significant); yellow = no evidence of effect; grey = no data available for this outcome in this subgroup

⊕◯◯◯= very low certainty of evidence

⊕⊕◯◯= low certainty of evidence

⊕⊕⊕◯= moderate certainty of evidence

⊕⊕⊕⊕ = high certainty of evidence

Table s6 – GRADE assessment of all outcomes

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Whole blood | Blood component | Relative (95% CI) | Absolute (95% CI) | | |
| **24-hour mortality** | | | | | | | | | | | | |
| 2 (Cotton 2013, Gruenwald 2008) | randomised trials | very serious [a] | not serious | not serious | very serious [b,c] | none | 6/86 (7.0%) | 5/85 (5.9%) | **OR 1.15** (0.33 to 4.03) | **8 more per 1,000** (from 39 fewer to 142 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **24-hour mortality - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 6/55 (10.9%) | 5/52 (9.6%) | **OR 1.15** (0.33 to 4.03) | **13 more per 1,000** (from 62 fewer to 204 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **24-hour mortality - Non trauma (surgery)** | | | | | | | | | | | | |
| 1 (Gruenwald 2008) | randomised trials | serious [e] | not serious | not serious | very serious [c] | none | 0/31 (0.0%) | 0/33 (0.0%) | **RD 0.00** (-0.06 to 0.06) [f] | **0 fewer per 1,000** (from 60 fewer to 60 more) [f] | ⊕◯◯◯ VERY LOW | CRITICAL |
| **30-day mortality** | | | | | | | | | | | | |
| 3 (Cotton 2013, Gruenwald 2008, Robertson 1975) | randomised trials | very serious [a] | serious [g] | not serious | very serious [b] | none | 17/241 (7.1%) | 15/224 (6.7%) | **OR 1.02** (0.32 to 3.26) | **1 more per 1,000** (from 45 fewer to 123 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **30-day mortality - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 12/55 (21.8%) | 7/52 (13.5%) | **OR 1.79** (0.65 to 4.98) | **83 more per 1,000** (from 43 fewer to 302 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **30-day mortality - Non-trauma (surgery)** | | | | | | | | | | | | |
| 2 (Gruenwald 2008, Robertson 1975) | randomised trials | very serious [h] | not serious | not serious | very serious [b,c] | none | 5/186 (2.7%) | 8/172 (4.7%) | **OR 0.55** (0.17 to 1.71) | **20 fewer per 1,000** (from 38 fewer to 30 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Kidney injury (AKI/ARF) - Trauma** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Whole blood | Blood component | Relative (95% CI) | Absolute (95% CI) | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 1/55 (1.8%) | 1/52 (1.9%) | **POR 0.94** (0.06 to 15.32) [i] | **1 fewer per 1,000** (from 18 fewer to 212 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Heart injury - CHF - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 1/55 (1.8%) | 0/52 (0.0%) | **POR 7.00** (0.14 to 353.16) [i] | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Heart injury - New onset arrhythmia - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 3/55 (5.5%) | 1/52 (1.9%) | **POR 2.64** (0.36 to 19.32) [i] | **30 more per 1,000** (from 12 fewer to 256 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Lung injury - TRALI - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [c] | none | 0/55 (0.0%) | 0/52 (0.0%) | **RD 0.00** (-0.04 to 0.04) [f] | **0 fewer per 1,000** (from 40 fewer to 40 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Lung injury - ARDS - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 0/55 (0.0%) | 1/52 (1.9%) | **POR 0.13** (0.00 to 6.45) [i] | **17 fewer per 1,000** (from 19 fewer to 93 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Lung injury - pulmonary oedema - Non-trauma (surgery)** | | | | | | | | | | | | |
| 1 (Shackford 1981) | randomised trials | serious [j] | not serious | not serious | very serious [c] | none | 0/14 (0.0%) | 0/14 (0.0%) | **RD 0.00** (-0.13 to 0.13) [f] | **0 fewer per 1,000** (from 130 fewer to 130 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Hospital LOS – trauma (days, median [IQR])** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | very serious [k] | not serious | not serious | very serious [c] | none | N=55 Median 15 (IQR 7-28) | N=52 Median 14 (IQR 7-23) | | Median difference 1 day more | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Hospital LOS – non-trauma (surgery) (days, median [range])** | | | | | | | | | | | | |
| 1 (Gruenwald 2008) | randomised trials | serious [e] | not serious | not serious | very serious [c] | none | N=31 Median 12 (range 6-36) | N=33 Median 18 (range 7-79) | | Median difference 6 days less | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Mechanical ventilation LOS – trauma (days, median [IQR])** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Whole blood | Blood component | Relative (95% CI) | Absolute (95% CI) | | |
| 1 (Cotton 2013) | randomised trials | very serious [k] | not serious | not serious | very serious [c] | none | n=55 Median 0 (IQR 0-4) | N=52 Median 0 (IQR 0-4) | - | Median difference 0 | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Mechanical ventilation LOS - Non-trauma (surgery) (hours)** | | | | | | | | | | | | |
| 1 (Moritz 2000) | randomised trials | serious [l] | not serious | not serious | very serious [c,m] | none | 30 | 30 | - | MD **2.33 lower** (8.5 lower to 3.84 higher) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Mechanical ventilation LOS – Non-trauma (surgery) (hours, median [range])** | | | | | | | | | | | | |
| 1 (Gruenwald 2008) | randomised trials | serious [e] | not serious | not serious | very serious [c] | none | N=31 Median 119 hours (range 28-480) | N=33 Median 164 hours (range 54-912) | - | Median difference 45 hours less | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Oxygen dependence LOS - Non-trauma (surgery) (hours)** | | | | | | | | | | | | |
| 1 (Vasan 2021) | randomised trials | serious [l] | not serious | not serious | very serious [c,n] | none | 30 | 35 | - | MD **5.91 lower** (10.83 lower to 0.99 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **ICU/ITU/HDU LOS – trauma (days, median [IQR])** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | very serious [k] | not serious | not serious | very serious [c] | none | N=55 Median 0 (IQR 0-19) | N=52 Median 1 (IQR 0-13) | - | Median difference 1 day less | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **ICU/ITU/HDU LOS - Non-trauma (surgery) (hours)** | | | | | | | | | | | | |
| 2 (Moritz 2000, Vasan 2021) | randomised trials | serious [l] | not serious | not serious | very serious [c] | none | 60 | 65 | - | MD **7.1 lower** (12.89 lower to 1.31 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **ICU/ITU/HDU LOS - Non-trauma (surgery) (days, median [range])** | | | | | | | | | | | | |
| 1 (Gruenwald 2008) | randomised trials | serious [e] | not serious | not serious | very serious [c] | none | N=31 Median 5 (range 3-20) | N=33 Median 7 (range 1-39) | | Median difference 2 days less | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Infections** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Whole blood | Blood component | Relative (95% CI) | Absolute (95% CI) | | |
| 2 (Cotton 2013, Gruenwald 2008) | randomised trials | very serious [a] | serious [b] | not serious | very serious [b,c] | none | 14/86 (16.3%) | 15/85 (17.6%) | **OR 0.91** (0.40 to 2.05) | **13 fewer per 1,000** (from 98 fewer to 129 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Infections - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 11/55 (20.0%) | 9/52 (17.3%) | **OR 1.19** (0.45 to 3.17) | **26 more per 1,000** (from 87 fewer to 226 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Infections - Non-trauma (surgery)** | | | | | | | | | | | | |
| 1 (Gruenwald 2008) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 3/31 (9.7%) | 6/33 (18.2%) | **OR 0.48** (0.11 to 2.13) | **85 fewer per 1,000** (from 158 fewer to 139 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Sepsis - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [b,c] | none | 2/55 (3.6%) | 1/52 (1.9%) | **POR 1.86** (0.19 to 18.33) [i] | **16 more per 1,000** (from 16 fewer to 245 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Arterial/thrombotic event (MI, stroke, cerebrovascular events) - Trauma** | | | | | | | | | | | | |
| 1 (Cotton 2013) | randomised trials | serious [d] | not serious | not serious | very serious [c] | none | 0/55 (0.0%) | 0/52 (0.0%) | **RD 0.00** (-0.04 to 0.04) [f] | **0 fewer per 1,000** (from 40 fewer to 40 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Transfusion reaction - febrile - Non-trauma (surgery)** | | | | | | | | | | | | |
| 1 (Robertson 1975) | randomised trials | very serious [p] | not serious | not serious | very serious [b] | none | 1/155 (0.6%) | 1/139 (0.7%) | **POR 0.90** (0.06 to 14.46) [i] | **1 fewer per 1,000** (from 7 fewer to 88 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |

***CI:*** *Confidence interval;* ***IQR****: inter-quartile range;* ***OR:*** *Odds ratio;* ***MD:*** *Mean difference;* ***POR:*** *Peto odds ratio*

*GRADE Explanations (footnotes)*

a. *Downgraded 2 levels due to high ROB or multiple unclear domains across all categories spread over included studies for this outcome*
b. *Downgraded 2 levels due to wide 95%CI: spreads beyond default threshold of 25% for benefit or harm (0.75 to 1.25)*
c. *Downgraded 2 levels due to small sample size (optimal information size N>400)*
d. *Downgraded 1 level due to baseline imbalance (adequate allocation concealment and unclear sequence generation), high ROB in blinding unlikely to affect objective outcomes*

*e. Downgraded 1 level due to unclear method of randomisation (block randomisation), and unclear patient flow (assumed to be ITT analysis)*
*f. Risk difference due to zero cases in both groups*
*g. Downgraded 1 level due to moderate heterogeneity: different direction of effect by subgroup (trauma/non-trauma); i2+=57%*
*h. Downgraded 2 levels due to high or unclear ROB in majority of domains across all included studies for this outcome*
*i. Peto OR due to low event rate*
*j. Downgraded 1 level due to lack of information on blinding, allocation concealment, and patient flow (analysis method)*
*k. Downgraded 2 levels due to baseline imbalance (despite adequate allocation concealment and sequence generation), and high ROB in blinding (LOS as non-objective outcome)*
*l. . Downgraded 1 level due to unclear ROB in all domains*
*m. Downgraded 1 level due to 95%CI crossing lower boundary for minimally important difference (0.5*SD in control group =+/-6.52)*
*n. Downgraded 1 level due to 95%CI crossing lower boundary for minimally important difference (0.5*SD in control group = +/-5.51)*
*o. Downgraded 1 level due to different direction of effect by subgroup (trauma/non-trauma); i2=0%*
*p. Downgraded 2 levels due to quasi-RCT (no true randomisation), and unclear blinding*

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